

## Remarks

In the Office Action mailed August 25, 2004, the Office rejected all of the pending claims, i.e., claims 1-4, 6-10, 12, 14-16, and 29. The Office asserts that the pending claims are unpatentable over Ameta et al. (while the Office does not provide a cite, Applicant assumes the reference is to the Ameta et al. publication from *Asian Journal of Chemistry Reviews*, 1(2):106-124 (1990)), which was provided to the Office in an Information Disclosure Statement; the Office is respectfully requested to clarify the cite in future communications so that the written record is clear) in view of “the acknowledged prior art,” Colic (U.S. Patent No. 6,544,401), and Beattie et al. (U.S. Patent No. 5,364,344).

### Colic

Applicant notes that Colic issued as a U.S. Patent after Applicant’s effective filing date but was filed April 28, 2000 and claims priority to a provisional patent application filed April 29, 1999. Applicant invented the claimed subject matter before the effective date of Colic, as demonstrated by the attached Declaration under 37 C.F.R. § 1.131. Thus, Colic is not available as a reference against the claimed invention.

### Claim Rejections – 35 U.S.C. § 103

Applicant submits that the rejection is untenable as presented, and is even more untenable in the absence of Colic, which Applicant has antedated.

The Office relies on Ameta et al., which is alleged to disclose that “singlet oxygen can be prepared by photosensitization in which oxygen is passed into a solution containing a dye and a substrate exposed to visible or u.v. light or by the reaction between sodium hypochlorite and hydrogen peroxide in which the other products are NaCl and water.” The photosensitization reaction described by Ameta et al. is at the heart of photodynamic therapy, which Applicant has

described in the Background section of the application (see, for example, paragraphs [009]-[016]). The reaction between sodium hypochlorite and hydrogen peroxide to yield singlet oxygen, with water and sodium chloride as by-products, was described by Foote and Wexler in 1964 (see, for example, paragraphs [017] and [018] of the specification).

The Office asserts that Applicant acknowledges that singlet oxygen is effective against tumor cells and cancer (citing paragraph [009], which relates to photodynamic therapy, referred to above), but that there are drawbacks of those methods (citing paragraphs [013]-[015], which describe the drawbacks of photodynamic therapy, also referred to above). The Office states that Applicant discloses that the singlet oxygen produced by photodynamic therapy is identical to that produced by hypochlorite and peroxide (citing paragraph [017], also referred to above). The Office asserts that Applicant acknowledges that singlet oxygen is an oxidizing component of human neutrophils (citing paragraph [019]). Finally, the Office asserts that Applicant acknowledges that singlet oxygen is short-lived (citing paragraph [084]).

The Office cites Colic, but as noted above, Colic has been antedated and its disclosure is now irrelevant. The Office cites Beattie et al. as teaching a dual lumen catheter, which can be used for delivering different fluids into a bloodstream.

In the absence of Colic, the question is whether the claimed invention is obvious over Ameta et al. in view of the “acknowledged” prior art and Beattie et al. Structured in this way, the outstanding rejection is almost identical to that made in the Final Office Action, on which Applicant made appeal. Applicant respectfully maintains that the claimed invention is not obvious.

### **The Differences Between the Pending Claims and the Prior Art**

Applicant's claim requires *administration of at least one source of peroxide and at least one source of hypochlorite to allow for the generation of singlet oxygen* at the target site. The prior art fails to teach the administration of hypochlorite and the administration of peroxide, in combination, to produce singlet oxygen at a target site.

### **The Rejection**

The Office rejects the pending claims over Ameta et al. in view of "acknowledged prior art" and Beattie et al. The Office refers to alleged acknowledged prior art that relates to 1) photodynamic therapy and the attendant production of singlet oxygen by photo-oxidation of dye compounds (referring to paragraphs [009], [013], [014], and [015]), and 2) other background information relating to singlet oxygen, such as the fact that it can be made by a hypochlorite-peroxide reaction, that it is short-lived, and that it is found in human neutrophils.

#### Ameta et al.

This document is a review article relating to the chemistry of singlet oxygen. It notes that singlet oxygen can be produced in a variety of ways, including physical methods such as photosensitization, and chemical methods such as by reacting sodium hypochlorite with hydrogen peroxide. Ameta et al. also describes the lifetime of singlet oxygen in various solvents, including water, in which the lifetime is on the order of microseconds.<sup>1</sup>

But what Ameta et al. also clearly states, and what the Office fails to note, is that singlet oxygen is also released from the solid adducts formed in reaction between triaryl phosphite and ozone at low temperature, that it is a decomposition product of superoxide, that preoxyacetyl

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<sup>1</sup> Applicant notes that the specification suggests (at paragraph [084], for example) that singlet oxygen lifetime is an order of magnitude less, i.e., nanoseconds. This difference is not believed to impact any determination of patentability and is believed to result from differing published reports on the lifetime value.

nitrate decompose in the presence of alkali to give singlet oxygen, that organic peracids decompose in alkaline solutions to produce singlet oxygen, and that singlet oxygen is generated by the adsorption and decomposition of ozone on silica gel. And beyond the chemical methods, Ameta et al. states that singlet oxygen can be created by electrodeless microwave or radiofrequency discharge in an oxygen environment.

While the Office cites Ameta et al. for the discussion of producing singlet oxygen by photosensitization or by the hypochlorite-peroxide reaction, in fact, the authors give no more attention to the reaction of hypochlorite and peroxide to produce singlet oxygen than they do to any other topic. When one reads the entire document, one sees that the authors spend at least two pages discussing the *photodynamic effects* of some organic compounds. (See Ameta et al., pages 117 and 118.) They state that the discovery that microorganisms are killed by light in the presence of oxygen and a sensitizing dye is called “photodynamic action” and includes cell damage, induction of mutations or cancer, and ultimate death. They point out that these “effects are due to photo-oxidation of various sensitive cell constituents.” (*Id.*, page 117.)

While Ameta et al.’s discussion is generally related to the chemistry of singlet oxygen, to the extent that it does extend to biological applications of that chemistry, those discussions relate to photochemical reactions and photodynamic effects. If Ameta et al. can be said to suggest any biological application, it is photodynamic therapy.

“Acknowledged” Prior Art

The Office cites to several paragraphs from Applicant’s application that discuss photodynamic therapy in animals. Photodynamic therapy generally involves infusing a photoactive compound into a patient and allowing the compound to collect in a tumor that is to be targeted. The photoactive compound in the tumor is then irradiated with light energy to

produce singlet oxygen in the target site. There are drawbacks to photodynamic therapy, which include targeting problems as well as expense. But photodynamic therapy does not involve, or relate to the use of, either peroxide or hypochlorite.

The Office cites to paragraph [017] of Applicant's specification for the proposition that the singlet oxygen made by photodynamic therapy is identical to that produced by reacting hypochlorite with peroxide. But that fact does not lead from one method of production to the other. As noted to Ameta et al., there are at least six chemical methods for making singlet oxygen, any of which would appear equally attractive. There is no reason a person skilled in the art would choose any particular method. And, as noted above, when Ameta et al. discusses singlet oxygen in the context of biological applications, it discusses photodynamic therapy.

The Office also cites to Applicant's application (paragraph [019]) for the premise that singlet oxygen is recognized as being naturally present in humans. Applicant's discussion in this section of the application simply describes what was believed to be current hypotheses on the functioning of eukaryotic cells. These cells are believed to produce, through complicated enzymatic processes, hydrogen peroxide, hypochlorite, singlet oxygen, and other potent oxidizing compounds in connection with phagocytic activities. But this understanding of basic cell biology does nothing to teach or suggest Applicant's claimed invention.

U.S. Patent No. 5,364,344 to Beattie et al.

The Office cites to Beattie et al. for the teaching of a dual lumen catheter. Dual lumen catheters, such as those described by Beattie et al., can be used for a number of purposes, including administration of two separate solutions.

Applicant submits that the teaching of Beattie et al. no more suggests the present invention than it does administering vinegar and baking soda for an effervescent effect. There is

nothing in Beattie et al. that suggests any particular compounds or substances for administration. Beattie et al. simply provides a means for administering two solutions simultaneously, *if one wanted to do so*. But given the art, there is no reason that one would want to administer at least one source of peroxide and at least one source of hypochlorite.

In the Office Action, the Office states that “one of ordinary skill in the art would expect that by use of a dual lumen catheter the peroxide and hypochlorite could be kept separate until the last possible moment thereby ensuring the maximum concentration of singlet oxygen possible.” (Office Action, page 5, lines 4-7.) Applicant respectfully submits that none of the art relied upon by the Office suggests that peroxide and hypochlorite should be administered together for treating a mammal. Thus, it is irrelevant that one *could* use a dual lumen catheter. And the suggestion that one would use such a catheter to ensure “the maximum concentration of singlet oxygen possible” is completely unsupported.

### **Applicant’s Argument**

#### **Obvious to Try is Not the Proper Standard**

Applicant’s claimed invention stems from the discovery that while toxic and potentially harmful if delivered alone, hypochlorite and peroxide can be delivered to react to form singlet oxygen. Singlet oxygen exhibits a powerful oxidizing effect, but is short-lived. The reaction products of sodium hypochlorite and hydrogen peroxide *in vivo*, thus, are short-lived singlet oxygen, sodium chloride, and water. When administered in this manner, the effect is specific to the local area, with little possibility for collateral damage. Indeed, Applicant has observed that what collateral damage does occur to normal cells is quickly reversed. While the oxidative effects are permanent on abnormal cells, the normal cells in the area are able to reproduce and

heal the treated area. This surprising effect could not have been predicted, and would not have been expected given the prior art teachings.

Applicant's claims require the administration of hypochlorite *and* peroxide, but the Patent Office does not cite a single teaching that suggests administration of *either reactant*. Prior to Applicant's invention no one had ever simultaneously or sequentially injected peroxide and hypochlorite into a living animal, not to mention with the desired effect of producing singlet oxygen, and not to mention with the desired outcome of killing cancer cells. While it was known that hypochlorite and peroxide would react to form singlet oxygen *in vitro*, no one knew or suggested that it could or should be done *in vivo*. Indeed, prior to Applicant's actual reduction to practice, it could not possibly have been known what the actual result would be. One could not have predicted that a desirable effect would be achieved.

Nevertheless, the Office asserts that the claimed invention is obvious. It asserts, based on the known *in vitro* reaction between hypochlorite and peroxide to produce singlet oxygen, the natural existence of short-lived singlet oxygen in humans, and the understanding that singlet oxygen is the active agent in photodynamic therapy of tumors, that it would have been obvious to treat a tumor by administering hypochlorite and peroxide. What the Office is suggesting here is that it would have been obvious to try: obvious to experiment with the reactants, hoping that a desirable outcome would be achieved, or obvious to test what would happen if the reactants were administered. But obvious-to-try is not the standard for determining whether an invention would have been obvious and the Federal Circuit has repeatedly warned against it.

#### A Simple Invention

As discussed in the application, photodynamic therapy involves administering a photoreactive dye compound, so that the compound is localized in the area to be treated, and

selectively exposing the area to light, so that the photoreactive dye produces singlet oxygen. Applicant's invention also produces singlet oxygen at a target site, but does so much more simply: the compounds react to produce singlet oxygen at the target site without the need for photons to initiate the reaction. As compared to other methods, Applicant's invention is relatively simple.

Because of the simplicity of Applicant's invention, special care should be exercised to avoid an improper hindsight approach. "When the art in question is relatively simple, . . . the opportunity to judge by hindsight is particularly tempting. Consequently, the tests of whether to combine references need to be applied rigorously." *McGinley v. Franklin Sports, Inc.* 262 F.3d 1339, 1351, 60 U.S.P.Q.2d 1001 (Fed. Cir. 2001). *See in re Kotzab*, 217 F.3d 1365, 1371, 55 U.S.P.Q.2d 1313 (Fed. Cir. 2000) ("With this simple concept in mind, the Patent and Trademark Office found prior art statements that in the abstract appeared to suggest the claimed limitation. But, there was no finding as to the specific understanding or principle within the knowledge of a skilled artisan that would have motivated one with no knowledge of [the inventor's] invention to make the combination in the manner claimed.") Applicant respectfully submits that the Office has been lulled into a hindsight approach to considering the obviousness of the claimed invention because of its relative simplicity, and this is improper.

The Cited Art Teaches Away From the Claimed Invention

Finally, Applicant respectfully notes that at the time this application was filed, it was widely recognized and accepted in the medical profession that peroxide and hypochlorite were toxic and should not be administered. Attached hereto is a printout from the American Cancer



Society website that includes statements regarding the use of hydrogen peroxide.<sup>2</sup> The American Cancer Society's position on hydrogen peroxide, which it recommends to all physicians and patients, was stated best when the Society said: "Although hydrogen peroxide is well known for its antiseptic properties, there is no evidence that it has value as a treatment for cancer or other diseases."

As the Federal Circuit has repeatedly recognized, proceeding contrary to the accepted wisdom in the art represents "strong evidence of unobviousness." *In re Hedges*, 783 F.2d at 1041, 228 U.S.P.Q. at 687; *W.L. Gore & Assocs., Inc. v. Garlock, Inc.*, 721 F.2d at 1552, 220 U.S.P.Q. at 312 (prior art teaching that conventional polypropylene should have reduced crystallinity before stretching and should undergo slow stretching, led away from claimed process of producing porous article by expanding highly crystalline PTFE by rapid stretching); accord *In re Fine*, 837 F.2d at 1074, 5 U.S.P.Q. at 1599. And where a reference warns against rather than teaches an invention, one of skill in the art cannot be expected to combine it with another teaching. *Id.*

Applicant respectfully submits that the art, as represented in the cited statements above, clearly suggests that one *not* administer peroxide for treatment of cancer. The accepted wisdom among medical practitioners, i.e., people of ordinary skill, was to avoid administration of peroxide for treatment of cancer. This is very strong evidence of the non-obviousness of the present invention, which requires, among other things, administration of at least one source of peroxide to a target site.

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<sup>2</sup> This document was provided to the Office as an Attachment to Applicant's Response filed January 28, 2004.

The Supreme Court case of *Graham v. John Deere*, 383 U.S. 1, 148 U.S.P.Q. 459 (1966), mandates that in considering obviousness, one must consider not only the scope and content of the prior art, but also, the level of ordinary skill in the art. In this instance, where the claim relates to methods of treating a mammal, those of ordinary skill will be medically trained. A basic tenet of medical training, be it human or veterinary, is do no harm to a patient. Thus, patient safety is a very real concern to those of ordinary skill in this art. And a medical practitioner, with the toxicity information provided by Schraufstatter et al. (of record, and discussed in prior responses and the Appeal Brief) and the advisory provided by the American Cancer Society, would not be motivated to administer peroxide to a patient.

Statements regarding hypochlorite use are best summarized in the Material Safety Data Sheet for sodium hypochlorite, from the Clorox Company ("Health Hazard Data" section), a copy of which is provided as an attachment.<sup>3</sup> Based on the warnings in this MSDS, hypochlorite is clearly regarded as a toxic substance. Applicant respectfully submits that one of skill in the art would not have administered at least one source of hypochlorite for treatment of cancer, given that the compound was known to be so toxic.

The Office states that it acknowledges Applicant's arguments with respect to the toxicity of these agents, but that "Applicant's evidence does not disclose a composition in which peroxide and hypochlorite are present or discuss the toxicity of the combination of peroxide and hypochlorite." (Office Action, page 6, lines 7-9.)<sup>4</sup> With respect, Applicant points out that the

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<sup>3</sup> This document was also provided to the Office as an Attachment to Applicant's Response filed January 28, 2004.

<sup>4</sup> Moreover, so that the written record is clear, the "evidence" referred to by the Office refers to documents provided by Applicant in pointing out the Office's failure to make a *prima facie* case of obviousness. It is not secondary "evidence" of nonobviousness.

claim requires “administering at least one source of peroxide *and* at least one source of hypochlorite anion to the target site to be treated, wherein the at least one source of peroxide and at least one source of hypochlorite are from separate sources.” The claim does not require administration of a “combination” or “composition in which peroxide and hypochlorite are present.”

In sum, the art clearly establishes that peroxide and hypochlorite are toxic and potentially dangerous, and the American Cancer Society, while recognizing its antiseptic qualities, actually advises *against* the administration of peroxide in treating cancer or any other disease. It is also submitted that the absence of a similar caution against the use of hypochlorite may be telling in that no one has ever even advocated its administration, so a warning is unnecessary. It is respectfully submitted that the prior art clearly teaches away from the presently claimed invention.

Thus, in view of the art, there is simply no reason one would be motivated to arrive at the presently claimed invention.

### **Conclusion**

Applicant’s claimed invention stems from the discovery that while believed to be toxic and potentially harmful if delivered alone, hypochlorite and peroxide can be delivered to react to form short-lived singlet oxygen, sodium chloride, and water, at a desired target site. When administered in this manner, the effect is specific to the local area, with little possibility for collateral damage.

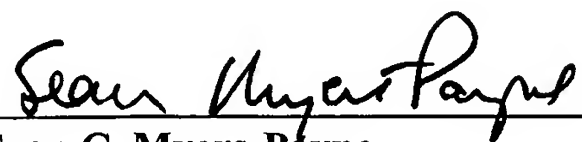
Applicant respectfully submits that the Office has failed to establish a *prima facie* case of obviousness with regard to claims 1-4, 6-10, 12, 14-16, and 29. A Notice of Allowance is earnestly requested.

*Application No. 10/051,121*  
*Attorney Docket No. 29794/04001*  
*Response*

If there is any fee due in connection with the filing of this Response, please charge the fee to our Deposit Account No. 03-0172.

Respectfully submitted,

Date: November 22, 2004

  
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**Amendments to the Drawings**

In the Office Action mailed August 25, 2004, the Office objected to Figures 12-18 for being of poor quality. In response, Applicant submits herewith Replacement Sheets for Figures 12-18. The content of the Figures shown in the Replacement Sheets is the same as that in the originally filed drawings and no changes have been made; however, the quality is improved.

Applicant respectfully submits that the Replacement Sheets satisfy the drawing requirements and requests the withdrawal of the objection.